PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference DC/4-32652A/NFI 8027	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/13715	International filing date *(day/month/year)* 04.12.2003	Priority date *(day/month/year)* 05.12.2002
International Patent Classification (IPC) or both national classification and IPC G01N33/53		
Applicant NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.06.2004	29.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Schmidt, Harald Telephone No. +31 70 340-4023

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/13715

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-62	as originally filed

Claims, Numbers

1-16	as originally filed

Drawings, Sheets

2/6-6/6	as originally filed
1/6	received on 04.06.2004 with letter of 02.06.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 3-16 (all completely)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 3-16 (all completely)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1 and 2 .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1,2
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,2
Industrial applicability (IA)	Yes:	Claims	1,2
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item I
Basis of the report

The sheets of drawings (numbered as from page 76 to page 81), including the amended sheet numbered as page 20, should be re-numbered as from sheet 1/6 to sheet 6/6 to meet the requirements of Rule 11 PCT.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Since the international search was performed for the first invention only due to an objection against unity of invention (see below), no opinion with regard to novelty, inventive step and industrial applicability is raised for subject-matter of claims 3 to 16.

Re Item IV
Lack of unity of invention

The problem underlying the present application resides in the provision of labeled proteins or labeled peptides.
As a solution, labeled peptides or labeled proteins are prepared that comprise an affinity tag and a labeling residue.
The technical feature in the sense of Rule 13.2 PCT which a priori could unify different solutions is the entity of being a peptide or protein comprising an affinity tag and a labeling residue.
However, peptides or proteins comprising an affinity tag and a labeling residue have already been described in the prior art, see e.g. the publication by Conrads TP et al. (2001) Anal. Chem. 73: 2132-2139, disclosing affinity isolation of a radioactively labeled Cys-polypeptide (see pages 2133 and 2134).
The single general concept in the sense of Rule 13.1 PCT is thus the notion that the labeled compounds of the present application are of high purity.
The special technical feature is hence a compound having a reactive group A, a label containing residue B and an affinity tagging group C as defined in claim 3.

This special technical feature of invention 2 is lacking as limiting feature in invention 1, since A, B, and C are not specified in the compounds of invention 1.
Therefore, the invention of group 1 relates to a class of labeled compounds that is broader than the compounds of invention 2.
Invention 1 and 2 do hence not meet the requirements of Rule 13 PCT.
As there are no other features which could fulfil the role of a special technical feature in the sense of Article 13.2 PCT, the present application is found to lack unity of invention, giving rise to the subjects as follows:

Invention 1: Claims 1 and 2
method for providing a labeled target protein or labeled target peptide

Invention 2: Claims 3 to 16
labeled compounds and their use and methods

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 02/052271 A (NOVARTIS ERFIND VERWALT GMBH ; NOVARTIS AG (CH); QUINN DOUGLAS FREDERI) 4 July 2002 (2002-07-04)
D2: CONRADS TP ET AL.: "Quantitative Analysis of Bacterial and Mammalian Proteomes Using a Combination of Cysteine Affinity Tags and 15N-Metabolic Labeling" ANALYTICAL CHEMISTRY, vol. 73, no. 9, 1 May 2001 (2001-05-01), pages 2132-2139, XP002290302
D3: WO 02/28890 A (SCRIPPS RESEARCH INST ; BARK STEVEN J (US); HAHN KLAUS M (US)) 11 April 2002 (2002-04-11)

The present application does not meet the criteria of Article 33(1) PCT, because the

subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.

The document D1 discloses a method for providing a labeled target protein or labeled target peptide, wherein a Cys-containing peptide is labeled using an isotope-coded affinity tag; it is further mentioned that the labeled peptide is isolated using avidin affinity chromatography (see pages 12 to 14).
Therefore, subject-matter of claim 1 does not meet the requirements of Article 33(2) PCT.

The document D2 discloses a method for providing a labeled target protein or labeled target peptide, wherein a soluble Cys-polypeptide is labeled with iodoacetyl PEO-biotin and isolated using a packed avidin column (see page 2133, left-hand column - page 2134, right-hand column).
Therefore, subject-matter of claim 1 does not meet the requirements of Article 33(2) PCT.

The document D3 discloses a method for providing a labeled target protein or labeled target peptide, wherein a peptide having a carboxy-terminal $(His)_6$ tag is labeled with tetramethylrhodamine N-hydroxy-succinimidyl ester and purified using gel filtration/RP-HPLC (see page 28, line 20 - page 29, line 3).
It is noted that a short C-terminal peptide sequence (e.g. GAA) of the peptide disclosed in D3 is considered to be a (cleavable) linker.
Therefore, subject-matter of claim 1 does not meet the requirements of Article 33(2) PCT.

Dependent claim 2 does not contain any features which, in combination with the features of any claim to which it refers, meet the requirements of the PCT in respect of novelty and/or inventive step, see documents D1 to D3 and the corresponding passages cited in the search report.

Fig 1